Medical Science

25(115), September, 2021

Anticardiolipin antibody level in hypertensive disorders of pregnancy and its association with pregnancy outcome

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To Cite:
Abdulwahhab EK, Al-Sakkal G. Anticardiolipin antibody level in hypertensive disorders of pregnancy and its association with pregnancy outcome. Medical Science, 2021, 25(115), 2268-2274

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Peer-Review History
Received: 22 July 2021
Reviewed & Revised: 24/July/2021 to 28/August/2021
Accepted: 30 August 2021
Published: September 2021

Peer-review Method
External peer-review was done through double-blind method.

ABSTRACT

Objective: Find out the association of anticardiolipin antibodies between normotensive hypertensive disorders of pregnancy and pregnancy outcome, and investigate the possibility of making anticardiolipin antibodies as a biomarker for hypertensive disorders of pregnancy involving preeclampsia. *Methods:* A case control study conducted at maternity teaching hospital in Erbil city. The participants were selected from the obstetrical outpatient clinic or from inpatients with matching age, body mass index and gestational age. *Results*: Seventy-four pregnant women were enrolled in the study; 34 of them were diagnosed with hypertensive disorders of pregnancy (case group) and the other 40 were healthy pregnant women (control group). There was no statistical significance between anticardiolipin antibodies between the two main study groups, and neither between severe and non-severe hypertensive pregnant women. Hypertensive pregnant women with positive anticardiolipin antibodies had significant association with preterm delivery and neonatal weight of below 2500g ($P < 0.05$). *Conclusions:* There is an association between anticardiolipin antibody and preterm labor and low birth weight in hypertensive pregnant women.

Keywords: Hypertensive disorders of pregnancy, preeclampsia, anticardiolipin antibody

1. INTRODUCTION

Hypertension in pregnancy is a common condition, affecting about 10% of pregnant women. A mother could already have chronic hypertension, either diagnosed prior to conception or during the first 19 weeks of gestation (<20 gestation), in addition to elevation of blood pressure related to pregnancy; gestational hypertension (GH) and preeclampsia (PE) (Webster et al., 2019). GH can be diagnosed if there is high blood pressure without proteinuria or other signs of organ dysfunction appearing de novo > 20 week of gestational age or within 48 to 72 hours of parturition and disappear by 12 weeks postpartum (Hacker et al., 2015). Half of mothers with GH are diagnosed between 24 to 35 weeks develop PE (Mammaro et al., 2009). Preeclampsia is best described as a pregnancy-specific syndrome that can affect virtually

every organ system. In addition, it heralds a higher risk for cardiovascular disease later in life (Gupte and Wagh, 2014). Developing proteinuria keeps being a significant diagnostic criterion, and is an objective marker and reflects the system-wide endothelial leak that characterizes the preeclampsia syndrome (Dashe et al., 2018).

The Anticardiolipin antibodies (aCL) could be seen in otherwise healthy individuals with an approximate prevalence between 1 to 5% (Mehrani and Petri, 2009), aCL are related to thrombophilia (both in arteries and/or veins) and with unfavorable obstetrical like recurrent spontaneous miscarriage, PE, intrauterine growth restriction (IUGR) and late fetal loss, which is a devastating event for both the family and obstetricians (Di Prima et al., 2011). The estimated incidence of pregnancy loss in patients with Antiphospholipid syndrome (APS) is 34% to 76%, and some evidence for positive aCL in cases with high-risk pregnancy, with a higher risk for pregnancy loss, while whether aCL associated with late pregnancy loss still remains controversial (Xu et al., 2019).

2. PATIENTS AND METHODS

Study design and setting

A prospective case control study enrolling 74 pregnant women, the first group involved 34 pregnant patients with hypertensive disorders of pregnancy and the second group involved 40 normotensive pregnant women. The study was done at maternity teaching hospital in Erbil city between January 2019 and December 2019.

Target population

Pregnant women with and without hypertensive disorders of pregnancy

Sample calculation and collection

A sample of 100 pregnant women (>20weeks of gestation) were allocated for follow-up, 50 healthy women and 50 with hypertensive disorders of pregnancy. Twenty-six participants were lost to follow-up, so the total sample size was 74, as shown in Figure 1.

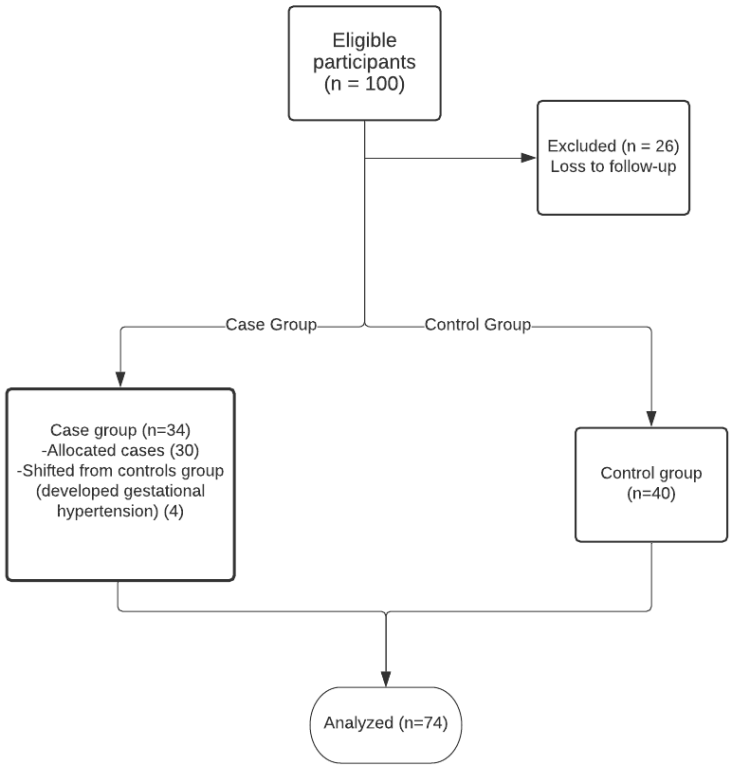

Figure 1 Participant's flowchart

Patients' examination and follow-up

A full medical, obstetrical, gynecological history and clinical examination was obtained from each patient including particularly general information such as maternal age, BMI, blood pressure at first antenatal visit, gravidity, parity, number of miscarriage or

stillbirth, history of hypertension or any other chronic illness and family history of hypertension. The pregnant women were selected from the obstetrical outpatient clinic or from those who has been admitted to ward. Follow up was done till one month after delivery. Blood samples were obtained from each patient and sent for routine and specific investigations including: Complete blood count, Liver function tests, Blood urea and serum creatinine, Serum albumin, Urinary protein, IgM and IgG anticardiolipin antibodies

Exclusion criteria

Systemic illnesses other than hypertension, history of smoking or substance abuse, use of anti-inflammatory medications

Measurement

Anticardiolipin antibodies (IgM and IgG) was measured by enzyme linked immune sorbent assay ELISA using AESKULISA Cardiolipin-GM kit uses purified cardiolipin with native human ß2-glycoprotein I.

Statistical analysis

The data were handled with Statistical package for social sciences (SPSS) version 26. Independent t-test (two tailed) was used to examine the difference in the mean of continuous variables among study groups accordingly. Fisher's Exact Test was used to examine the association between categorical variables among study groups. A level of P – value less than 0.05 was considered significant.

3. RESULTS

The distribution of involved participant and comparison between study groups by general characteristics is shown in tables (1 and 2). The age of participant was ranging from 17 to 46 years with a mean of 27.68 and standard deviation of ± 6.89 years. In study groups, (case and control) the highest proportion of pregnant women had the age between 21 – 30 years (44.1% and 55% respectively). In regards to BMI level, 38.2% of hypertensive pregnant women and 50% of normotensive pregnant women were overweighed. In terms of gravidity, the largest proportion of pregnant women (61.8% of hypertensive pregnant women and 67.5% of normotensive pregnant women) had history of pregnancy between (1 -3) times. Concerning parity, the largest percentage of participant had (1 – 3) children 44.1% of hypertensive pregnant women and 22% of normotensive pregnant women.

Table 1 Distribution of participant by general characteristics.

Variables	Hypertensive Pregnant women (%) n=34	Normotensive pregnant women (%) n=40	Total n=74
Age (Years)			
≤20	7 (20.6)	6 (15)	13 (17.6)
21 - 30	15 (44.1)	22 (55)	37 (50)
≥31	12 (35.3)	12 (30)	24 (32.4)
BMI Level			
Normal(18.5-25)	12 (35.3)	13 (32.5)	25 (33.8)
Overweight(2530)	13 (38.2)	20 (50)	33 (44.6)
Obese(>30)	9 (26.5)	7 (17.5)	16 (21.6)
Gravidity			
1 - 3	21 (61.8)	27 (67.5)	48 (64.9)
>3	13 (38.2)	13 (32.5)	26 (35.1)
Parity			
0	11 (32.4)	11 (27.5)	22 (29.7)
1 - 3	15 (44.1)	22 (55)	37 (50)
>3	8 (23.5)	7 (17.5)	15 (20.3)

Table 2 reveals the results of both study groups who have been tested for IgG and IgM anticardiolipin antibodies. Number of participant with positive IgG and IgM anticardiolipin antibodies were higher in the hypertensive pregnant women study group but there was no statistical significance between the two groups (P = 0.415 for IgG and 0.170 for IgM).

Table 2 Comparison of Anticardiolipin antibodies results between normotensive and hypertensive pregnant women

Variables		Group		Total	P-Value
		Hypertensive Pregnant women (%) n=34	Normotensive pregnant women (%) n=40		
IgG result count	Negative	26 (42.6)	35 (57.4)	61 (100.0)	0.415
	Equivocal	2 (50.0)	2 (50.0)	4 (100.0	
	Positive	6 (66.7)	3 (33.3)	9 (100.0)	
	Total count	34 (45.9)	40 (54.1)	74 (100.0)	
IgM result count	Negative	26 (41.3)	37 (58.7)	63 (100.0)	0.170
	Equivocal	3 (75.0)	1 (25.0)	4 (100.0)	
	Positive	5(71.4)	2 (28.6)	7 (100.0)	
	Total count	34 (45.9)	40 (54.1)	74 (100.0)	

** Fisher's Exact Test was conducted for this analysis*

Table 3 and shows the results of anticardiolipin antibody testing among severe and non-severe hypertensive pregnant woman. Proportion of patients with positive IgG or anticardiolipin antibody were more in participants with severe hypertension but there was no statistical significance between the severe and non-severe hypertension patients (P=0.066, 0.141 respectively).

Table 3 Comparison of Anticardiolipin antibodies result between severe and non-severe hypertensive pregnant women

Variables		Hypertension Group		Total	P-Value
		Severe	Non-Severe		
IgG result count	Negative	9 (34.6)	17 (65.4)	26 (100.0)	0.415
	Equivocal	1 (50.0)	1 (50.0)	2 (100.0)	
	Positive	5 (83.3)	1 (16.7)	6 (100.0)	
	Total count	15 (44.1)	19 (55.9)	34 (100.0)	
IgM result count	Negative	9 (34.6)	17 (65.4)	26 (100.0)	0.170
	Equivocal	2 (66.7)	2 (66.7)	3 (100.0)	
	Positive	4 (80.0)	1 (20.0)	5 (100.0)	
	Total count	15 (44.1)	19 (55.9)	34 (100.0)	

** Fisher's Exact Test was conducted for this analysis*

The total count and percentage of anticardiolipin testing in different types of hypertensive disorders of pregnancy is shown in Figure 2 and 3. The highest share for positive anticardiolipin antibody test lies within preeclampsia group but there is no statistical association between anticardiolipin IgG and IgM results and types of hypertensive disorders of pregnancy (P = 0.285, and 0.380, respectively).

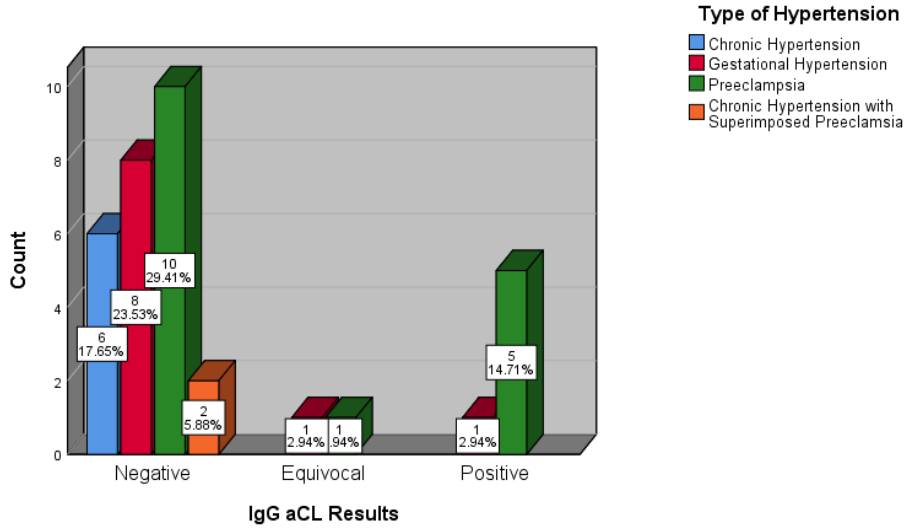

Figure 2 Distribution of case group according to types of hypertension and IgG aCL results

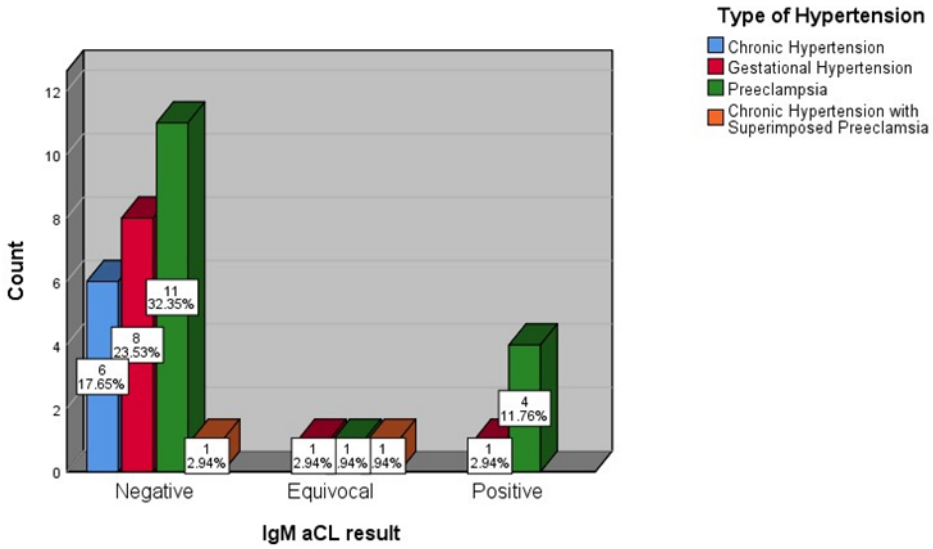

Figure 3 Distribution of case group according to types of hypertension and IgM aCL results

Table 4 shows the association of pregnancy outcome (in terms of caesarian delivery, preterm delivery, fetal weight below 2500g and perinatal death) and anticardiolipin antibodies results. Regarding IgG and IgM aCL, there was statistical association with regards to preterm labour and neonatal weight of below 2500g within hypertensive pregnant women (P = 0.001 and 0.016 for IgG – P = 0.002 and 0.037 for IgM respectively) while there was no significant association with regards to caesarian section and perinatal death (P = 1.000 and 0.355 for IgG – P = 0.818 and 0.406 for IgM respectively). Concerning double positive aCL (both IgG and IgM positive), there was a statistical significance regarding preterm delivery only with a P value of 0.005.

Table 4 Comparison of Anticardiolipin antibody result and pregnancy outcome

Outcomes in case-group	Anticardiolipin antibody status					
	IgG aCL	P value	IgM aCL	P value	Double positive aCL	P value
Caesarian section	6.5%	1.000	3.2 %	0.818	3.2 %	1.000
Preterm delivery	16.1%	0.001	12.9 %	0.002	12.9 %	0.005
Neonatal weight<2500g	9.7 %	0.016	6.5 %	0.037	6.5 %	0.112
Perinatal death	3.2%	0.355	3.2 %	0.406	3.2 %	0.301

Fisher's Exact Test was conducted for this analysis

4. DISCUSSION

Hypertension in pregnancy is significantly associated with maternal and fetal suffering and death (Di Prima et al., 2011). The definition, classification and terminology of these disorders are still controversial which refers to the fact that the understanding of this disorder is still questionable and much more research regarding this disorder is mandatory (Braunthal and Brateanu, 2019). Anticardiolipin antibodies, a family member of antiphospholipid antibodies, are groups of antibodies directed against phospholipids and their presence has been connected to fetal loss and thrombosis in several articles (Carmo-Pereira et al., 2003). It is believed that these antibodies may be involved in the genesis of GH and especially preeclampsia, via triggering the coagulation pathway (Dreyfus et al., 2001; Lockshin, 1994). In our study, we found that the level of anticardiolipin antibodies has no significant difference between normotensive and hypertensive pregnant women (P = 0.415, 0.170 for IgG and IgM respectively). This result goes with (Kaur et al., 2017) and (Uncu et al., 1996) studies that concluded the same result while (Allen et al., 1996) and (do Prado et al., 2010) study found an association between aCL and preeclampsia. By comparing anticardiolipin antibody results between non-severe and severe hypertension pregnant women, we found in our study that IgG and IgM and double positive aCL results had no significant association between these two groups (P = 0.066, 0,141 and 0.146 respectively) which agrees with (Yamada et al., 2009) and (Marchetti et al., 2016) studies. The study also states that multiple antiphospholipid antibodies positivity along side with aCL may increase the risk for severe hypertensive disorders of pregnancy.

Regarding Anticardiolipin antibodies and different types of hypertension, we found in our study the there was a higher number of preeclamptic pregnant women have positive anticardiolipin antibodies (IgG and IgM aCL) but it was not of statistical significance (P = 0.570 and 0.380 respectively). Another finding in our study when comparing maternal or fetal outcome with aCL is that positive IgG or IgM aCL within the hypertensive group was associated significantly with higher proportion of preterm labor and neonatal weight of below 2500g (P = 0.001 and 0.016 for IgG P= 0.002 and 0.037 for IgM). Double positive aCL was also associated with preterm labor (P = 0.005). These results agreed (Yamada et al., 2009) study results and (Carmo-Pereira et al., 2003). There was no such correlation with regards to caesarian section or perinatal death. It is difficult to correlate the pregnancy outcome and aCL results in hypertensive pregnant women as the preterm labor and low birth weight may be as a result of hypertension itself. But traditionally, aCL are prothrombotic factors that may affect placental and spiral artery in which may result in such poor outcome.

It is not clear for the moment the exact pathophysiology for the effect of anticardiolipin on pregnancy and the presence of anticardiolipin itself is not sufficient to cause such an effect. Many studies focus on the second hit hypothesis in which the effect of aCL is activated by oxidative stress, trauma, inflammation or other factors which lead eventually to activate the immune system and coagulation pathways. Pregnancy itself is considered as a state of oxidative stress and this status is exacerbated by hypertension (Antovic et al., 2018). When looking at our study, we may find some limitations; small sample size with diverse types of this disorder, another limitation is related to ELISA testing as many factors may influence the results such as laboratory or manufacture variables (Pierangeli and Harris, 2008).

5. CONCLUSION

An association exists between anticardiolipin antibody with preterm labor and low birth weight in hypertensive pregnant women. No association was found when comparing anticardiolipin antibodies neither among normotensive and hypertensive pregnant women nor between severe and non-severe hypertensive pregnant women.

Author contribution

Eman Kamal Abdulwahhab: Conception and design of the work, the acquisition, analysis, and interpretation of data for the work, and Drafting the work.

Ghada Al-Sakkal: Conception and design of the work, interpretation of data for the work, and revising it critically for important intellectual content

Informed consent

Written informed consent was obtained from all individual participants included in the study. Additional informed consent was obtained from all individual participants for whom identifying information is included in this manuscript.

Ethical approval for human

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards (Code: 2019/C081).

Conflicts of interest

The authors declare that they have no conflict of interest.

Funding

This study has not received any external funding.

Data and materials availability

All data associated with this study are present in the paper.

REFERENCES AND NOTES

1. Allen JY, Tapia-Santiago C, Kutteh WH. Antiphospholipid antibodies in patients with preeclampsia. Am J Reprod Immunol 1996; 36(2):81-5.
2. Antovic A, Sennström M, Bremme K, Svenungsson E. Obstetric antiphospholipid syndrome. Lupus Sci Med 2018; 5(1):e000197.
3. Braunthal S, Brateanu A. Hypertension in pregnancy: Pathophysiology and treatment. SAGE Open Med 2019; 7:2050312119843700.
4. Carmo-Pereira S, Bertolaccini ML, Escudero-Contreras A, Khamashta MA, Hughes GRV. Value of IgA anticardiolipin and anti-β2-glycoprotein I antibody testing in patients with pregnancy morbidity. Ann Rheum Dis 2003; 62(6):540-3.
5. Dashe JS, Bloom SL, Spong CY, Hoffman BL. Williams Obstetrics, 25th Edition: McGraw-Hill Education; 2018.
6. Di Prima FAF, Valenti O, Hyseni E, Giorgio E, Faraci M, Renda E, De Domenico R, Monte S. Antiphospholipid Syndrome during pregnancy: the state of the art. J Prenat Med 2011; 5(2):41-53.
7. Do Prado AD, Piovesan DM, Staub HL, Horta BL. Association of anticardiolipin antibodies with preeclampsia: a systematic review and meta-analysis. Obstet Gynecol 2010; 116(6):1433-43.
8. Dreyfus M, Hedelin G, Kutnahorsky R, Lehmann M, Viville B, Langer B, Fleury A, M'Barek M, Treisser A, Wiesel M-L. Antiphospholipid antibodies and preeclampsia: a case-control study. Obstet Gynecol 2001; 97(1):29-34.
9. Gupte S, Wagh G. Preeclampsia-eclampsiaJ Obstet Gynaecol India 2014; 64(1):4-13.
10. Hacker NF, Gambone JC, Hobel CJ. Hacker & Moore's Essentials of Obstetrics and Gynecology: Elsevier Health Sciences; 2015.
11. Kaur G, Pahwa S, Kaur A, Nagpal M. A comparative study of the serum levels of antiphospholipid antibodies in hypertensive disorder of pregnancy and normotensive pregnancy. Int j reprod contracept obstet gynecol 2017; 6(2):581.
12. Lockshin MD. Antiphospholipid antibody: future developments. Lupus 1994; 3(4):309-11.
13. Mammaro A, Carrara S, Cavaliere A, Ermito S, Dinatale A, Pappalardo EM, Militello M, Pedata R. Hypertensive disorders of pregnancy. J Prenat Med 2009; 3(1):1.
14. Marchetti T, De Moerloose P, Gris J-C. Antiphospholipid antibodies and the risk of severe and non-severe pre-eclampsia: the NOHA case-control study. J Thromb Haemost 2016; 14(4):675-84.
15. Mehrani T, Petri M. Chapter 2 epidemiology of the antiphospholipid syndrome. In: Cervera R RJ, Khamashta M, editor. Handbook of Systemic Autoimmune Diseases Amsterdam, Netherlands: Elsevier; 2009. p. 13-34.
16. Pierangeli SS, Harris EN. A protocol for determination of anticardiolipin antibodies by ELISA. Nat Protoc 2008; 3(5):840-8.
17. Uncu G, Ozan H, Küąükerdoğan Is, Cengiz C. Anticardiolipin antibodies in pregnancy induced hypertension. Eur J Obstet Gynecol Reprod Biol 1996; 70(1):97-100.
18. Webster K, Fishburn S, Maresh M, Findlay SC, Chappell LC. Diagnosis and management of hypertension in pregnancy: summary of updated NICE guidance. BMJ 2019; 366.
19. Xu J, Chen D, Duan X, Li L, Tang Y, Peng B. The association between antiphospholipid antibodies and late fetal loss: A systematic review and meta-analysis. Acta Obstet Gynecol Scand 2019; 98(12):1523-33.
20. Yamada H, Atsumi T, Kobashi G, Ota C, Kato EH, Tsuruga N, Ohta K, Yasuda S, Koike T, Minakami H. Antiphospholipid antibodies increase the risk of pregnancy-induced hypertension and adverse pregnancy outcomes. J Reprod Immunol 2009; 79(2):188-95.